CURRENT DOSE RECOMMENDATIONS FOR PONATINIB IN CHRONIC MYELOID LEUKEMIA PATIENTS CAN DIMINISH ADVERSE EVENTS WHILE MAINTAINING EFFICACY

Author(s): Valentin Garcia-Gutierrez, Juan Carlos Hernandez-Boluda, Beatriz Moiraghi, Elżbieta Szczepanek Tomasz Sacha,Carolina Pavlovsky, Olga Grzybowska-Izydorczyk, Juan Correa, Raul Perez Lopez, Elżbieta Patkowska Joanna Góra-Tybor,Andres Novo Garcia, Santiago Osorio Prendes, Rolando Vallansot, Angel Ramirez Payer, Ewa Wasilewska, Miguel Piris Villaespesa,Concepcion Boque Genovard, Manuel Perez Encinas, Antonio Jimenez Velasco, Fermin Sanchez-Guijo, Mario Andres Romo Collada,Maria Teresa Gomez Casares, Guillermo Orti Pascual, Maria Soledad Duran, Angeles Portero, Maria Isabel Mata, Maria Soledad Noya, Gonzalo Caballero, Nuria Garcia, Diego Robles de Castro, Maria Jose Ramirez, Alicia Senin Magan, Sunil Lakhwani,Juan Manuel Alonso Dominguez, Maria Isabel Montero, Maria Jose Lis Chulvi, Hanna Ciepłuch, Juan Luis Steegman

Abstract: PS1186

Type: Poster Presentation

Presentation during EHA24: On Saturday, June 15, 2019 from 17:30 - 19:00

Location: Poster area

Background

Ponatinib has been established as an optimal salvage treatment option in chronic myeloid leukemia (CML) patients. Serious adverse events, mainly cardiovascular (CVS) events, have been related to ponatinib use at the standard dose (45 mg/day). Clinical trials are currently evaluating different dose schemes in order to answer whether dose modifications could diminish side effects while maintaining responses.

Aims

To evaluate the efficacy and safety of ponatinib treatment in the real life-setting.

Methods

We have performed an International observational retrospective study collecting information from CML patients treated with ponatinib between 2014 and 2018. The indication of ponatinib, as well as its dose schedule, was made according to the criterion of the attending physician. Molecular biology tests were performed according to ELN guidelines and BCR-ABL/ABL ratios were expressed as % IS in all centers. Treatment responses were calculated with the patients at risk at each specific time points. For progression free survival (PFS) calculation, progression was defined as transformation to the advances phases. For the event free survival (EFS), the events were treatment discontinuation due to any reason, progression or death. Data collection followed the local regulations for observational studies.

Results

73 CML patients treated with ponatinib according to clinical practice in Spain, Poland, and Argentina, were included in the study. Patients had received a median of 2.8 TKIs prior to ponatinib treatment, with a median time of 43 months from CML diagnosis to ponatinib start. Median age at diagnosis was 58 years and Sokal prognostic risk score was low, intermediate, high, and unknown in 28%, 21%, 31%, and 20% of the patients. Patients were treated while in chronic phase (84%), accelerated phase (10%), and blast crisis (6%). In total, 61% of the patients had cardiovascular risk factors at the time of starting ponatinib, 5 patients had suffered previous thrombosis, and 4 patients had a pathological ankle-brachial index. BCR-ABL mutations were present in 33 patients (23 of them harbored the T315I mutation). Ponatinib starting dose was 45mg, 30mg, and 15mg in 60%, 20%, and 20% of the patients, respectively. Drug dosage was

diminished in 21/45 (46%) of the patients who started on 45mg/day and in 4/14 (28%) patients who started on 30mg/day. In contrast, 50% (7/14) of the patients who started on ponatinib 15mg/day increased dose during follow up. Rates of Complete hematological responses, complete cytogenetic responses, and major molecular responses by 12 months (table 1) were 100%, 52%, and 45% respectively. Overall, 56% of patients improved previous response, 32% maintained the same degree of response, whereas 12% lost the baseline responses. With a median follow-up of 24 months, 35 patients (48%) discontinued treatment due to toxicity (38%), stem cell transplantation (21%), death (17%) or lack of efficacy (24%). Most frequent toxicities leading to treatment discontinuations were severe cardiovascular events, hepatotoxicity, and myelotoxicity (table 2). Severe cardiovascular events were seen in 10 patients (9%). The majority of patients (70%) experiencing cardiovascular events had more than 2 CVS risk factors before ponatinib start. EFS, PFS, and overall survival was 46%, 69% and 83% at 21 months.

Table 1. Treatment responses at specific time points

	3 months		6 months		12 months		18 months	
	N	%	N	%	N	%	N	%
CHR	64	100	54	100	42	100	28	100
CCyR	30	46	330	55	22	52	19	67
MMR	16	25	25	46	19	45	15	53
MR4	4	6	14	25	13	31	12	42
MR.5	3	4	8	14	10	23	10	35

CHR: Complete hematological response; CCyR: Complete cytogenetic response; MMR: Major molecular response; MR4: Molecular response grade 4; MR4.5: molecular response grade 4.5

Table 2. Grade 3-4 side effect related to ponatinib

	n	%
Toxicities that led to treatment discontinuations		
Cardiovascular events	7	9
Peripheral occlusive arterial disease	1	1
Popliteal thrombosis	1	1
Isquemic heart disease	3	4
Cerebrovascular disease	1	1
Pulmonary hypertension	1	1
Liver toxicity	3	4
Hematological toxicity	3	4
Grade 3-4 toxicities		
Cardiovascular events	10	13
Peripheral occlusive arterial disease	5	6
Popliteal thrombosis	1	1
Isquemic heart disease	2	3
Cerebrovascular disease	2	3
Liver toxicity	7	10
Hypertension	4	5
Gastrontestinal	3	4
Anemia	5	7
Thrombopenia	13	18
Neutropenia	6	8

Conclusion

The present study demonstrates that the use of ponatinib in daily clinical practice under a dose limiting strategy in responding patients appears to be safe and preserves its clinical efficacy.

Session topic: 8. Chronic myeloid leukemia - Clinical

Keyword(s): Chronic myeloid leukemia, Therapy, Tyrosine kinase inhibitor